REMARKS

Objection to Specification

The Examiner rejected the specification, stating that Figures 14 and 15 contains a number of sequences but no indication as to the associated SEQ ID NOs. The Examiner states that sequence identifier must be used, "either in the drawing or in the Brief Description of the Drawings."

Applicants submit that the specification has already been amended to indicate the SEQ ID NOs. associated with each of the sequences of Figures 14 and 15. For example, in a response to comply with sequence listing requirement filed February 9, 2001, Applicants have amended the Brief Description of the Drawings in the specification as follows:

1. On page 32, line 13, after "present in mutant 28." please insert --Sequence assignments are as follows: 4: SEQ ID NO: 21; 10: SEQ ID NO: 22; 13: SEQ ID NO: 23; 16: SEQ ID NO: 24; 18: SEQ ID NO: 25; 19: SEQ ID NO: 26; 28: SEQ ID NO: 27; 34: SEQ ID NO: 28; 41: SEQ ID NO: 29; 33: SEQ ID NO: 30; 48: SEQ ID NO: 31; 55: SEQ ID NO: 32; 64: SEQ ID NO: 33; Jdf3: SEQ ID NO: 34.--.

2. On page 32, line 16, after "location of a mutation", please insert -- Sequence assignments are as follows: 4: SEQ ID NO: 35; 10: SEQ ID NO: 36; 13: SEQ ID NO: 37; 16: SEQ ID NO: 38; 18: SEQ ID NO: 39; 19: SEQ ID NO: 40; 28: SEQ ID NO: 41; 34: SEQ ID NO: 42; 41: SEQ ID NO: 43; 33: SEQ ID NO: 44; 48: SEQ ID NO: 45; 55: SEQ ID NO: 46; 64: SEQ ID NO: 47; Jdf3: SEQ ID NO: 48.--.

Applicants submit that Amendment 1 assigns SEQ ID NOs. 21-34 to sequences in Figure 14 and SEQ ID NOs. 35-48 to sequences in Figure 15. Applicants enclose a copy of the above February 9, 2001 response concurrently with the present response, as well as a returned post card from the Patent Office for the Examiner's convenience.

Based on the above, Applicants respectfully request the objection to the specification due to the sequences contained in Figures 14 and 15 be withdrawn.

Clarification of the Status of Claims 90-92 and the 35 U.S.C. 112 First Paragraph Rejection

Applicants had a telephone interview with the Examiner on April 5, 2004 to clarify the inconsistent status of claim 90-92 as indicated on the Office Action summary and the detailed Office Action. Applicants treat claim 90-92 as being rejected and address the objections and rejections on these claims in relevant sections below. Applicants also clarified with the Examiner that the 35 U.S.C. 112, first paragraph rejections as set forth on pages 5-6 of the Office Action are based on written description. A separate statement of substance will be submitted summarizing the entire content of the interview.

Claim Objections

Claims 89-92, 99, 104, 111, 112, 114, 117-121 are objected to because of the following informalities:

Claim 92 is objected to because of the recitation "praline (P) to leucine (L)." Applicants have corrected the clerical error and change the recitation to "proline (P) to leucine (L)." Solely for purpose of expediting the prosecution of the present application, applicants withdraw claim 92 and will pursue the subject invention of claim 92 in a later to-be-filed continuation application.

Claims 89-92, 99 and 104 are objected to because of the recitation of "one or more amino acids in exo I (DXE) motif." Applicants have adopted the Examiner's suggestion and amended claims 90 and 92 to recite "one or more amino acids in the exo I (DXE) motif." Solely for purpose of expediting the prosecution of the present application, applicants withdraw claims 89-92, 99 and 104 and will pursue the subject invention of claims 89-92, 99 and 104 in a later to-be-filed continuation application.

Claims 96, 97, 100-102 and 105 are objected to because of the recitation of "exo II" or "exo III." Applicants have amended the claims to recite "the exo II" or "the exo III." Solely for purpose of expediting the prosecution of the present application, applicants withdraw claims 96, 97, 100-102 and 105 and will pursue the subject invention of claims 96, 97, 100-102 and 105 in a later to-be-filed continuation application.

The Examiner suggested that ***claim 111*** should be amended for clarity because of its recitation of "wherein said mutation at one or more amino acids is at L408 or P410." Applicants have amended claim 111 to recite "further comprising a mutation at L408 and/or P410" solely for purpose of expediting the prosecution of the present application. Claims reciting "region II" will be prosecuted in a later to-be-filed continuation application.

The Examiner has objected to ***claim 114*** for its recitation of "LDF-3 DNA polymerase." Applicants have corrected the above clerical error so that the amended claim 114 recited "JDF-3 DNA polymerase."

Claims 117-121 are objected to because of the recitation of "sequence ID NO: 2." Applicants have amended claims 117-121 to recite "SEQ ID NO: 2."

Claims 111-112 are objected because they depend from rejected claim 110. Applicants have amended claims 111-112 to depend from claim 108 or 109.

Applicants believe the above amendments would overcome the claim objections on claims 89-91, 99, 100-102, 104-105, 111-112, 114, and 117-121. Applicants respectfully request the objections be withdrawn.

Claim Rejections under 35 U.S.C. 112, Second Paragraph

The Office Action states that claims 89-107, 113-114 and 122-125 are rejected for alleged indefiniteness.

Specifically, ***claims 89-107*** **(and claims 122-125 dependent on)** are rejected for reciting "exo I (DXE) motif." The Office Action states that SEQ ID NO.2 contains five different "DXE" motifs, and it is not clear what additional characteristics are for the exo I "DXE" motif. The Office Action further states that claims 96-97, 100, 102 and 105 are similarly rejected for the recitation of "exo II (NX2-3FD motif" and "exo III (YX3D) motif."

Applicants respectfully disagree. Applicants submit that the exo I, exo II, exo III motifs are well known in the art and the motifs are taught in the present specification. For example, the amended specification teaches on page 56:

> "DNA polymerases lacking 3'-5' exonuclease (proofreading) activity are preferred for applications requiring nucleotide analog incorporation (e.g., DNA sequencing) to prevent removal of nucleotide analogs after incorporation. The 3'-5' exonuclease activity associated with proofreading DNA polymerases can be reduced or abolished by mutagenesis. *Sequence comparisons have identified three conserved motifs (exo I (DXE), II (NX_{2-3}(F/Y)D), III (YX_3D)) in the 3'-5' exonuclease domain of DNA polymerases* (reviewed V. Derbyshire, J.K. Pinsonneault, and C.M. Joyce, Methods Enzymol. 262, 363 (1995)). Replacement of any of the conserved aspartic or glutamic acid residues with alanine has been shown to abolish the exonuclease activity of numerous DNA polymerases, including archaeal DNA polymerases such as Vent (H. Kong, R.B. Kucera, and W.E. Jack, J. Biol. Chem. 268, 1965 (1993)) and *Pfu* (Stratagene, unpublished). Conservative substitutions lead to reduced exonuclease activity, as shown for mutants of the archaeal 9° N-7 DNA polymerase (M.W. Southworth, H. Kong, R.B. Kucera, J. Ware, H. Jannasch, and F.B. Perler, Proc. Natl. Acad. Sci. 93, 5281 (1996))."

Thus, the specification as recited above specifically describes the structure of the exo motifs and their relationship to the function of exonuclease activity. Each of the exo motifs contains *only 3 to 6 amino acids*, among which 2-3 amino acids are conserved for family B DNA polymerases.

Solely for purpose of expediting the prosecution of the present application, Applicants have withdrawn claims 89-107 and Applicants will pursue the subject invention of claims 89-107 in a later to-be-filed continuation application.

Claims 99-107 are drawn to a recombinant family B DNA polymerase comprising a sequence as indicated by accession numbers as listed in Table II. Claims 99-107 are rejected for alleged indefiniteness because the Office Action states that accession numbers are subject to change.

Applicants respectfully disagree. Applicants submit that there are seventeen family B DNA polymerases listed in Table II (e.g., on pages 37-39). Each of the sequences in Table II is given its Genbank accession number, and each listed Genbank accession number *represents only one family B DNA polymerase sequence.* Claims 99-107 are limited to comprising one of the seventeen DNA polymerase sequences in Table II. Genbank accession number is well recognized in the art of recombinant DNA technology, one skilled in the art would have easily

known what the sequence for a family B DNA polymerase is as recited in claims 99-107 by using the accession numbers provided in Table II.

Solely for purpose of expediting the prosecution of the present application, Applicants have withdrawn claims 99-107 and Applicants will pursue the subject invention of claims 99-107 in a later to-be-filed continuation application.

Claims 93, 94, 113 and 114 are rejected for the recitation of "Y490" of SEQ ID NO. 2. Applicants have corrected the clerical error in the claims to recite "A490."

Applicants believe the above amendments should overcome the 35 U.S.C. 112, Second Paragraph rejections on claims 89-107, 113-114 and 122-125. Applicants respectfully request the rejections be withdrawn.

Claim Rejections under 35 U.S.C. 112, First Paragraph

The Office Action states that claims 89, 91 93-107 and 122-125 are rejected under 35 U.S.C. 112, first paragraph. Applicants, during a telephone interview with the Examiner on April 5, 2004, have clarified that the rejections are set forth for alleged lack of written description.

Claims 89, 91, 93-107 and 122-125 are rejected for the recitation of "further comprising a mutation at one or more amino acids in exo I (DXE) within." The Office Action states that the specification does not have support for the replacement of any of the exo motif residues other than D and E, more specifically, the specification does not have support for "X" residue.

Applicants specifically disagree. Applicants submit that the claims reciting "exo I (DXE)" are genus claims which encompass species of DNA polymerases containing one or more mutations at three specific amino acids locations, namely exo I (DXE), which makes the genus a relatively small one.

MPEP 2163 provides:

> "The written description requirement for a claimed genus may be satisfied through sufficient description of *a representative number of species* by actual reduction to practice..., reduction to drawings..., or *by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure,* or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.... See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A '*representative number of species*' means that *the species which are adequately described are representative of the entire genus.*" (*Emphasis added*)

The specification does describe exo I (DXE) domain and teaches mutations can be made within this domain, for example at D or E (e.g., on page 56 of the amended specification). For claims drawn to DNA polymerase comprising SEQ ID NO: 2, the specification further teaches four mutants within exo I which reduce 3' to 5' Exo activity (page 56). Applicants have also provided an actual reduction to practice of four individual embodiments, plus functional characteristics (i.e., reduced Exo activity) coupled with a known and disclosed correlation between function and structure. Applicants don't have to describe every and all species encompassed within the genus to meet the written description requirement.

Solely for purpose of expediting the prosecution of the present application, Applicants have withdrawn claims 89, 91, 93-107 and have amended claims 122-125 to depend from claim 2, 108 or 109. Applicants will pursue the subject invention of claims 89, 91, 93-107 in a later to-be-filed continuation application.

Claims 91, 93, 97-98, 101-102 and 110 are similarly rejected for the recitation of "a mutation at one or more amino acids in Region II (DXXSLYPSII)." The Office Action states that the specification does not support "for the mutation of any and all amino acid positions in Region II."

Applicants respectfully disagree. Applicants submit that the claims reciting "Region II (DXXSLYPSII)" are genus claims which encompass species of DNA polymerases containing

one or more mutations at ten specific amino acids locations, namely Region II (DXXSLYPSII), which makes the genus a relatively small one.

Tables V and VI on pages 74 and 75 of the specification describe the isolation and testing of 12 DNA polymerase mutants with mutations within this consensus region of SEQ ID NO: 2. Specifically, Table VI describes the isolation of 7 mutants with a primary mutation at L408 (3 are L408H, 4 are L408F) and 4 mutants with a primary mutation at P410 (all P410 L). Table V describes an additional P410L mutant (mutant p11). Thus, the specification provides 12 mutants, representing 3 different mutations within the Region II consensus sequence of SEQ ID NO: 2 as recited in claims 91-98, 110-121 and 126. Each of these mutants has a reduced discrimination against non-conventional nucleotides.

In addition to the description of the mutants in Tables V and VI, the specification provides additional description of numerous double mutants (a total of over 60 mutants are described in the specification). Ten such double mutants comprise at least one mutation within the Region II consensus region within the sequence of SEQ ID NO: 2. These include: L408H + A485T, L408F + A485T, and P410L + A485T described on page 15, lines 14-22; P410H + S345P and P410L + S345P on page 16, lines 1-3; L408H + V437 and L408H + L478 on page 17, lines 4-7; and A485T + Y409V, L408 mutation + Y409V and P410 mutation + Y409V. In all, five different amino acid mutations are described within the Region II consensus sequence recited in claim 10: L408H, L408F, P410L, P410H and P409V.

The specification further addresses the function of the Region II consensus structure of SEQ ID NO: 2 at page 52, where it states:

> "The domains of relevance in 17 of the 40 purified mutants were sequenced. Most randomly mutated clones contained more than one mutation in the regions sequenced but all mutants contained mutations at one of three sites. Mutations predicted to confer an enhanced ddNTP uptake phenotype were introduced into the progenitor exonuclease deficient DNA polymerase sequence by site-directed mutagenesis to eliminate ancillary mutations which were not expected to contribute to the improved dideoxynucleotide uptake phenotype.
>
> Sixteen of the seventeen JDF-3 DNA polymerase mutations were found in Region II (motif A) on either side of the tyrosine in the consensus sequence 404

DxxSLYPSII 413. These mutations consisted of DFRSLYLSII (P410L), DFRS**H**YPSII (L408H) and DFRS**F**YPSII (L408F)." (page 52, lines 13-23; **emphasis added**)

This passage shows that the mutations expected to have an effect on improved dideoxynucleotide uptake were centered in the Region II consensus sequence of SEQ ID NO: 2 as recited in claims 91-98, 110-123 and 126-127. This description provides a further structure/function correlation between the Region II consensus DXXSLYPSII and nucleotide discrimination. Applicants don't have to describe every and all species encompassed within the genus to meet the written description requirement.

Solely for purpose of expediting the prosecution of the present application, Applicants have withdrawn claims 91, 93, 97-98, 101-102 and 110 and will pursue the subject invention of claims 91, 93, 97-98, 101-102 and 110 in a later to-be-filed continuation application.

Claim 93 (claim 94 dependent on) is rejected for its recitation of "Y490", which is alleged not supported in the specification. Applicants have corrected the clerical error that claim 93 as amended now recites "A490."

In view of the above amendments, Applicants respectfully request the 35 U.S. C. 112, first paragraph, be withdrawn.

Rejoined Method Claims

Applicants would like to rejoin the subject matter as claimed in the method claims (i.e., claims 84, reproduced above) withdrawn from consideration due to a restriction requirement. For the purpose of clarity, Applicants add new method claims 131-147 to rejoin the subject matter. The newly added method claims contain all the limitations of the pending composition claims, e.g., claims 108-114. New claims are well supported in the specification as originally filed, e.g., on pages 11-22, 63-66, and 70-86. No new matters are added.

Applicants respectfully request the consideration of these rejoined claims.

CONCLUSION

Claims 1, 5, 108-109, 115-121 are allowed. Claims 111-127 are amended. Claims 89-107 and 110 currently withdrawn. Claims 128-147 are added. The amendments and new claims find support in the previous claims and in the specification, e.g., on pages 11-22, 63-66, and 70-86. No new matter is added.

Claims 1, 5, 108-109, 111-147 are currently pending in the application. Applicants submit that in view of the foregoing amendments and remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Sorge et al.
U.S. Serial No.:	09/698,341
Filed:	10/27/00
Entitled:	Compositions and Methods Utilizing DNA Polymerases

Group: 1655

Examiner: Sisson, B.

Attorney Docket No.: 25436/1560

BOX SEQUENCE
Commissioner for Patents and Trademarks
Washington, D.C. 20231

AMENDMENT AND RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Sir:

The following is submitted in response to the Notice to Comply With Requirements For Patent Applications Containing Nucleotide And/Or Amino Acid Sequence Disclosures mailed by the PTO on January 29, 2001.

In the Specification:

Please make the following amendments to the specification to incorporate SEQ ID Nos for the sequence listing submitted herewith.

1. On page 9, line 22, after "KX_3NSXYG", please insert --(SEQ ID NO: 5)--.
2. On page 10, line 1, after "$KX_3(F/Y)GX_2YG$", please insert --(SEQ ID NO: 6)--.
3. On page 10, line 8, after "$(KX_3(F/Y)GX_2YG$", please insert --SEQ ID NO: 6--.

4. On page 32, line 3, after "labeled oligonucleotide", please insert --(SEQ ID Nos: 18 and 19)--.

5. On page 32, line 13, after "present in mutant 28." please insert --Sequence assignments are as follows: 4: SEQ ID NO: 21; 10: SEQ ID NO: 22; 13: SEQ ID NO: 23; 16: SEQ ID NO: 24; 18: SEQ ID NO: 25; 19: SEQ ID NO: 26; 28: SEQ ID NO: 27; 34: SEQ ID NO: 28; 41: SEQ ID NO: 29; 33: SEQ ID NO: 30; 48: SEQ ID NO: 31; 55: SEQ ID NO: 32; 64: SEQ ID NO: 33; Jdf3: SEQ ID NO: 34.--.

6. On page 32, line 16, after "location of a mutation", please insert --Sequence assignments are as follows: 4: SEQ ID NO: 35; 10: SEQ ID NO: 36; 13: SEQ ID NO: 37; 16: SEQ ID NO: 38; 18: SEQ ID NO: 39; 19: SEQ ID NO: 40; 28: SEQ ID NO: 41; 34: SEQ ID NO: 42; 41: SEQ ID NO: 43; 33: SEQ ID NO: 44; 48: SEQ ID NO: 45; 55: SEQ ID NO: 46; 64: SEQ ID NO: 47; Jdf3: SEQ ID NO: 48.--.

7. On page 52, line 20, after "DxxSLYPSII 413", please insert --(SEQ ID NO: 7)--.

8. On page 52, line 21, after "DRFSLYLSII (P410L)", please insert --(SEQ ID NO: 8)--.

9. On page 52, line 21, after "DFRS**H**YPSII (L408H)", please insert --(SEQ ID NO: 9)--.

10. On page 52, line 21, after "DFRS**F**YPSII (L408F)", please insert --(SEQ ID NO: 10)--.

11. On page 53, line 9, after "KX_3NSXYG", please insert --(SEQ ID NO: 5)--.

12. On page 53, line 12, after "$KX_3(F/Y)GX_2YG$", please insert --(SEQ ID NO: 6)--.

13. On page 53, line 19, after "(KX_3(F/Y)GX_2YG", please insert --SEQ ID NO: 6--.

14. On page 57, line 4, after "GGG AAA **CAT ATG** ATC CTT GAC GTT GAT TAC", please insert --(SEQ ID NO: 11)--.

15. On page 57, line 6, after "GGG AAA **GGA TCC** TCA CTT CTT CTT CCC CTT C", please insert --(SEQ ID NO: 12)--.

16. On page 61, line 6, after "5' TCAGAT**GAATTC**GATGATCCTTGACGTTGATTAC 3'", please insert --(SEQ ID NO: 13)--.

17. On page 61, line 16, after "5' GAGA**GAATTC**ATAATGATAAGGAGGAA

AAAATTATGATCCTTGACGTTGATTAC3'", please insert --(SEQ ID NO: 14)--.

18. On page 61, line 19, after "5' TCAGAT**CTCGAG**TCACTTCTTCTTCCCCTTC 3'", please insert --(SEQ ID NO: 15)--.

19. On page 66, line 22, after "5' CCAGCTTTCCAGACTAGTCGGCCAAGGCC 3'", please insert --(SEQ ID NO: 16)--.

20. On page 66, line 23, after "5' AACTCTCGACCCGCTG 3'", please insert --(SEQ ID NO: 17)--.

21. On page 81, line 7, after "5' GGTTTTCCCAGTCACGACGTTGTAAAACGACGGCCAGT 3'", please insert --(SEQ ID NO: 18)--.

22. On page 83, line 12, after "5' GGTTTTCCCAGTCACGACGTTGTAAAACGACGGCCAGT 3'", please insert --(SEQ ID NO: 18)--.

23. On page 86, line 12, after "^{32}P-TAACGTTGGGGGGGGGCA→", please insert --(SEQ ID NO: 19)--.

24. On page 86, line 13, after "TGCAACCCCCCCCCGTAT", please insert --(SEQ ID NO: 20)--.

Applicants, in compliance with 37 C.F.R. 1.821(f), hereby state that the information recorded in computer readable form submitted herewith is identical to the written sequence listing. Applicants, in compliance with 37 C.F.R. 1.821(g), further state that the amendments add no new matter.

Respectfully submitted,

Date: 2/9/01

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Serial No. 09/698,341 File No. 25436/1560 By: KMW

Applicant(s): Gorf et al.

Title: Composition & Methods Utilizing DNA Polymerases

The Following, DUE_____ in the USPTO, was received by the PTO Mail Room on the date stamped hereon:

[✓] Cert. of Mailing by Express Mail (37 CFR 1.10)
Express Mail Label No. EL539766825US
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[ ] Patent Application (_____total pgs)
[ ] Provisional or [ ] Non-Provisional
(pgs) Specification, (pgs) Abstract,
(pgs) Claims (_____ # claims)
[ ] New Patent Application Transmittal
[ ] Provisional Patent Application Cover Sheet
[ ] Declaration and Power of Attorney
[ ] Drawings _____ Sheet(s) (FIGS._____)
[ ] Formal or [ ] Informal
[ ] Assignment of_____
[ ] Recordation Cover Sheet Form PTO-1595
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[ ] Form PTO 1449 and Copies of Cited References
[ ] Oath or Declaration of_____

[ ] Response to Notice to File Missing Parts
[ ] Copy of Part 2 of NFMP
[ ] Diskette Containing Nucleotide and/or Amino Acid Sequence Listing
[ ] Statement under 37CFR § 1.821 (f) and/or
[ ] Priority Document(s) #_____
[✓] Amendment/Response
[ ] Amendment Transmittal
[ ] Petition for Extension of Time (x2)
[ ] Check in the amount of _____
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MAILED 2/9/01

Docketed 2-12-04
Response due _____
Statutory Period _____
Fenwick & Dodge, LLP
Patent Department